
Systematic review methods for HuGE reviews

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Discussion meeting in Cambridge (UK)

Nov 2-3, 2004

- A joint meeting of HuGENet™ and Cambridge Genetics Knowledge Park
- To review and discuss methods for systematic review of gene-disease association studies
 - including gene-gene and gene-environment interactions

Purpose

- To update guidance for HuGE review authors
- To delineate a methodological research agenda



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Topics

- Study designs and bias
- Identifying studies
- Gene-gene and gene-environment interaction
- Meta-analysis, including
 - Hardy-Weinberg
 - Haplotypes
 - Individual participant data
- Interpretation
 - Reporting biases
 - Observational studies
 - Biomarkers and causality

Fields represented

- Epidemiology
- Human genetics
- Biostatistics
- Public health
- Systematic reviewing
- Information science / librarianship
- UK Biobank
- HuGENet™
- The Cochrane Collaboration

Key outcomes of workshop

To make HuGE reviews...

- **more systematic**
 - following methods of The Cochrane Collaboration
- **more comprehensive**
 - thorough searches for studies
 - continued incorporation of joint effects and biomarkers, where possible and relevant
 - increased awareness of risk of bias (within and among studies)
- **more quantitative**
 - encouraging meta-analysis
 - based on cross-tabulation of outcome by genotype

Continuum of types of review

Systematic reviews of the literature

- Majority of existing HuGE reviews



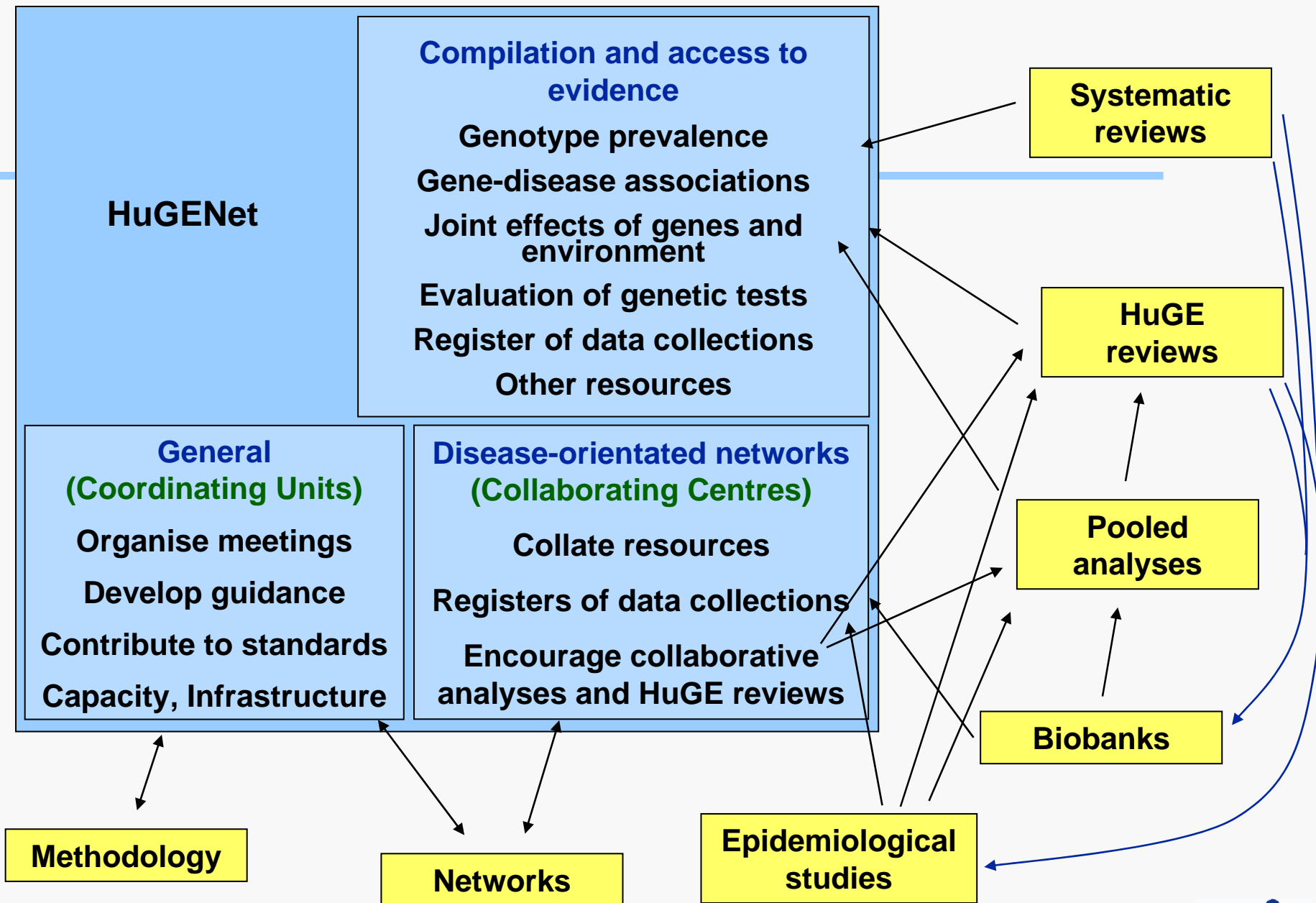
Pooled analyses

- Some existing HuGE reviews
- Initial focus of HuGE networks



- The (long term) future?
- Requires consistent, agreed format for on-line publication of results

Automated syntheses of epidemiological findings



Bias in individual studies

- **Variable susceptibility to bias (and information to assess it) - a problem in literature-based reviews**
 - **STROBE statement should help**
 - **Extension of STROBE with specific issues in gene-disease association identified as highly desirable**
- **No consensus on whether to restrict reviews to 'large' studies**
- **Typically very little information on which to judge accuracy of genotyping ('analytic validity')**
 - **Studies should report genotyping errors**

Gene-gene and gene-environment interaction

- Fundamental to understanding aetiology and for public health
- Very limited (likely misleading) when studies are not large
 - false-positive findings likely, and easy post hoc explanations
- Desire full cross-tabulations of data
 - typically only reasonable in pooled analyses, or with close collaboration of investigators
- Large-scale biobank studies have a key role to play here

Meta-analysis vs single studies

- **Debate in the clinical trials field over relative merits of mega-trials vs meta-analysis of small trials**
- **Meta-analyses provide information on variation in effects across populations, and on using different methods**
- **But beware reporting biases**
- **Should large-scale biobanks dwarf findings from smaller studies?**
- **HuGE reviews / meta-analyses should be used to inform studies on biobank data**